REMARKS

Applicants have amended claims 33 and 34 in a manner discussed at the recent interview.[1] In particular, claim 33 has been amended to require that the immunogenic polypeptide constitute only a fragment of the intact CETP protein ("about ten to no more than thirty amino acid residues of human CETP"). As discussed at the interview, support for this claim can be found in the specification in the paragraph bridging pages 15 and 16. Claim 34 also has been amended simply to make it a proper dependent claim, with a proper antecedent recitation, based in part on the new language in claim 33.

RESPONSE TO RESTRICTION

The Office Action of May 21, 2002 (Paper No. 23) requires that applicant elect between

(1) Any one of the antigenic carriers recited in claim 35 or 36, and

(2) Incomplete Freund's adjuvant or alum.

Applicants are not entirely clear on the basis and nature of the restriction. Nonetheless, in an attempt to provide a complete response, applicants elect the invention of Group (1) and as a species thereof identify tetanus toxoid.

INTERVIEW REPORT

Following the amendment, the claims now embrce a genus of CETP fragments and no longer include the entire, intact human CETP protein within the scope of the immunogenic polypeptide.

At the interview, Examiners Davis and Ungar identified an article by Evans (Evans et al., J. Lipid Res 35:1634-1645, 1994 – [A22]) as presenting a patentability issue that needed to be addressed on the record. This issue was discussed at the interview, with the Examiners and applicants' representatives outlining the bases on which the pending claims patentably distinguish the disclosure in Evans [A22]. Applicants hereby restate the bases on which the now-pending claims patentability differentiate Evans' teachings.

Evans [A22] is an example of a process of passive immunization using an antibody raised against a protein that is foreign to the host. Specifically, a monoclonal antibody (TP2) was isolated following injection of full-length (intact) human CETP into a mouse (using hybridoma technology). Human CETP has an amino acid sequence that differs from that of mouse CETP and was, accordingly, a protein foreign to mouse. TP2 (a mouse antibody raised against the intact human CETP) had been previously characterized as reacting with an epitope present on the full length native human CETP. Such epitope, at least in part, involved regions

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1 The pending claims have been renumbered 33-40. See paper 23.

mapping to the C terminus of human CETP.

As reported in Evans [A22], when this mouse TP2 antibody against full length human CETP was infused into a hamster, the hamster's CETP activity was inhibited to a degree greater than 60% and resulted in a 30-40 increase in HDL by four days post injection. Fourteen days after infusion, CETP activity and HDL levels returned to normal. Thus, these results suggest that the mouse TP2 antibody (raised against full length human CETP) had a sufficient affinity for the circulating hamster CETP (which has substantial homology with full length human CETP) to interfere with the hamster CETP activity in the short-term.

The invention claimed by Applicants can be distinguished from the teachings of Evans [A22] on several levels. Furthermore, the shortcomings in Evans' teachings are not rectified by reference to other documents, such as Jeung (Jeung et. al (Mol Cells 4:529-533, 1994 [A26]) either because one skilled in the art would not combine the documents due to their disparate teachings, or because such combinations still do not make obvious the full scope of applicants invention.

First and foremost, Examiner Ungar acknowledged and thus accepted the general principle that antibodies raised against a fragment of a protein do not predictably bind to the native protein. This concept is generally understood in terms of "epitope presentation" and "conformational epitopes." Accordingly, Examiner Ungar agreed that a teaching in the art showing an effect of antibodies raised against an intact protein (such as in Evans) is not predictive of the effects that antibodies raised only against limited protein fragments of the intact protein might exhibit (with respect to effects against the intact protein). In other words, a teaching of a successful result using an antibody raised against an intact protein (such as in Evans) does not suggest (or provide a skilled worker with a reasonable expectation) that one could obtain a similar result using an antibody raised against a fragment of the protein.

Evans' teaching that a mouse antibody to full length human CETP may be efficacious against the activity of hamster CETP *in vivo* does not even suggest that a mouse antibody raised to a fragment of CETP would have a similar effect in a hamster, let alone provide a basis for extrapolating the result in Evans to use of an antibody to a CETP fragment in a human patient. As a result, Evans' teachings do not disclose or suggest the process of the present invention. In applicants' invention a CETP immunogen having an exogenous antigenic carrier polypeptide that is peptide-bonded to an immunogenic polypeptide of a fragment of human CETP ("about ten to no

more than thirty amino acid residues of human CETP amino acid sequence"), rather than antibodies raised in a foreign animal, is used in an autoimmunization process.

On the basis of such prior art, it simply could not be predicted that injection of an immunogen containing a 10 to 30 amino acid residue corresponding to the C-terminal region of CETP in a human would (1) result in the production of antibodies and (2) that those antibodies would recognize the C-terminal region of endogenous intact CETP in a way that would interfere with the native activity of CETP. The activity of a foreign (exogenous) antibody raised against a mature protein is not predictive (provides no reasonable expectation) of being able to successfully raise, *in situ,* an antibody to a fragment of the protein that would possess the same activity. Indeed, based on such prior art, it could not even have been predicted that use of a human CETP fragment as part of an immunogen would even be immunogenic to a human, despite conjugation to a foreign carrier protein.

While the pending claims no longer include the full length, intact, human CETP within the scope of the immunogenic polypeptide, we submit that the short term passive immunization process of Evans [A22] also would not have made obvious the previously claimed active autoimmunization process and have amended the claims principally in the interest of expediting prosecution of this application. Applicants reserve the right to pursue the broader invention in another application.

In previous communications, *i.e.,* the Supplemental Communication (21 May 2002) and Third Preliminary Amendment (18 April 2002), Applicants distinguished their claimed invention from the closest passive immunization prior art (see summary table below) and will not burden the record with a detailed restatement of those differences.

Inventor	**Immunization**	**Infusant**
Applicant	Active	Autogenic peptide (self)
Swenson et al. [A19], Whitlock et al. [A21], Evans et al. [A22], Zuckerman et al. [A23]	Passive	Xenogenic antibody
Jeung et al. [A26]	Active	Xenogenic antigen (foreigb)

Suffice it to say, that the noted prior art of record simply does not establish that a skilled worker would have had a reasonable expectation that administering an inoculum to a human, in the

manner recited in the pending claims, would successfully lead to autoimmunization and the production of antibodies to cholesteryl ester transfer protein (CETP) -- with the result that the binding of the `antibodies to CETP would lessen the transfer of cholesteryl ester from HDL and increase the concentration of HDL cholesterol. Any extrapolation of the teachings directed to passive immunization processes to the present invention is unwarranted and would be based on a hindsight evaluation of the invention.

At the interview, there also was a suggestion that Evans might be combined with Jeung [A26]. Jeung [A26] describes using a 31 amino acid reside, C-terminal fragment of human CETP, conjugated to GST, to inoculate a rabbit. Jeung shows that the construct is immunogenic in rabbit. Importantly, Jeung does not teach that the resultant antibody is useful to alter HDL metabolism in the rabbit. In fact, Jeung does not even teach that such antibody is reactive to circulating host CETP. Thus, there is no proper basis for combining Evans with Jeung. In the absence of such teachings, such a combination would be based purely on a hindsight evaluation of these two documents with applicants' application as the road map.

Nor does the process described in Jeung itself provide a basis for rejecting the pending claims. Jeung's process can itself be readily distinguhed from the present invention because the immunogen used by Jeung is foreign (xenogenic) to the host. Jeung does not provide a reasonable expectation that one could administer an inoculum to a human, in the manner recited in the pending claims, and successfully obtain autoimmunization and the production of antibodies to cholesteryl ester transfer protein (CETP) -- with the result that the binding of the `antibodies to CETP would lessen the transfer of cholesteryl ester from HDL and increase the concentration of HDL cholesterol.

As a final matter, Examiner Ungar again raised the question of efficacy of applicants' claimed process. As noted at the interview, it has been confirmed in a publication subsequent to Applicants' invention (see Kwoh WO 96/39168, K02), using a rabbit model, that a C-terminal fragment, consisting of 10 amino acid residues of rabbit CETP, when injected with a carrier into rabbits, raises an immune response to CETP and raises HDL-C levels. See also Rittershaus WO 96/34888, B02, which shows that a C-terminal 31 amino acid fragment of human CETP, when injected with a carrier into rabbits, raises an immune response to CETP and raises HDL-C levels.

On the basis of the above, applicants respectfully request consideration of the subject application and allowance of the pending claims.

Please charge our Deposit Account No. 19-0733 for any fee.

Respectfully submitted,

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33. (Once Amended) A process for producing antibodies to cholesteryl ester transfer protein (CETP) in the blood of a human whose blood contains CETP, said process comprising the steps of:

(a) administering an inoculum to said human, said inoculum comprising a vehicle containing a CETP immunogen, wherein said CETP immunogen has (i) an exogenous antigenic carrier polypeptide that is peptide-bonded to (ii) an immunogenic polypeptide of about ten to no more than thirty amino acid residues ~~comprising amino acids 465 through 475~~ of human CETP amino acid sequence (SEQ ID NO: 28) and comprising amino acids 465 through 475 of human CETP amino acid sequence;

(b) repeating said administration, sufficient for said CETP immunogen to cause, by an autogeneic immunological response, production of antibodies which bind to CETP in the blood of said human and

(c) maintaining said antibodies which bind to CETP in the blood of said human by further administration of said inoculum,

whereby the binding of said antibodies to CETP in said blood lessens the transfer of cholesteryl ester from HDL and increases the concentration of HDL cholesterol in the blood of said human.

34. (Once Amended) The process of claim 33 wherein said amino acid residues of human CETP amino acid sequence of said immunogenic polypeptide ~~comprises~~ consists of amino acids 461 through 476 of human CETP amino acid sequence.